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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,307	01/14/2004	Melody A. Cobleigh	39740-0008A	5600

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HELLER EHRMAN LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CA 94025-3506

EXAMINER	
QIAN, CELINE X	
ART UNIT	**PAPER NUMBER**
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/758,307	COBLEIGH ET AL.	
	Examiner	Art Unit	
	Celine X. Qian Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-9,21-30,34,36-40,43-49,52,53 and 56-63* is/are pending in the application.

4a) Of the above claim(s) *22,34,38-40,43-49,52 and 56-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-9,21,23-30,36,37 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0305,0505,0206,0806*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 6-9, 21-30, 34, 36-40, 43-49, 52, 53, 56-63 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group I, and selected MYBL2 in the reply filed on 10/23/06 is acknowledged. The traversal is on the ground(s) that a search of all the groups would not be a serious burden. This is not found persuasive because the inventions are patentably distinct for reasons set forth in the previous office actions. A search of all the claims in a single application would have been burdensome. Therefore, the requirement is still deemed proper and is therefore made FINAL.

Since Applicants selected MYBL2 for examination, claims drawn to other genes or combination of genes will be withdrawn from consideration. Accordingly, claims 22, 34, 38-40, 43-49, 52, 56-63 are withdrawn from consideration for being directed to non-elected subject matter. Claims 1, 6-9, 21, 23-30, 36, 37 and 53 are currently under examination.

Claim Objections

Claim 23 is objected to for containing non-elected subject matter. Claim 23 depends on claim 22, which is drawn to non-elected subject matter. Amending the claims such that they are only directed to elected inventions is required. Examination of claim 23 is based on its dependency on claim 21.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 21, 25, 26, 29 and 30 are rejected under 35 U.S.C. 102(e) as being anticipated by Bertucci et al (US2003/0143539).

Bertucci et al. discloses a method comprising subject RNA extracted from a breast tissue obtained from the patient to gene expression analysis, determining the expression level of MYBL2, the expression level is normalized against a control gene, and creating a report summarizing the data obtained by said gene expression (see results in Table 5 on page 19, and 5A on page 20). Bertucci et al. also discloses a method of identifying genes that are related to sensitivity of anthracyclin (see Table 8 on page 24). Based on the data after statistical analysis and summarized in those tables (a table is one form of summarizing data in a report), one can predict the likelihood of long-term survival and treatment modality (for example, see page 28, [0125]-[0127]). Therefore, Bertucci et al. disclose the instantly claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 23, 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bertucci et al.

However, Bertucci et al. do not teach that the tumor sample is RNA from a fixed paraffin-embedded biopsy sample.

It would have been obvious to one of ordinary skill in the art to use statistical test such as Cox Proportional Hazards model to analyze the expression data obtained by the method taught by Bertucci et al. Such statistical data is well within the knowledge of ordinary artisan, and using such model to analyze data obtained by the method taught by Bertucci is within the capability of an ordinary artisan at the time the invention was made.

It would also have been obvious to one of ordinary skill in the art to use RNA obtained from fixed paraffin-embedded biopsy sample for analyzing gene expression taught by Bertucci et al. An ordinary skill in the art would use said sample because they are widely available in clinic because when a patient is diagnosed with the cancer, a biopsy would be done and fixed in paraffin for histological examination. The level of skill in the art is high. Obtaining RNA from fixed paraffin embedded tissue is routine work within the capability of an ordinary artisan. Applying a known method of obtaining RNA to the method taught by Bertucci is obvious to the ordinary skill in the art at the time the invention was made. Therefore, the claimed invention is *prima facie* obvious to an ordinary artisan at the time the invention was made.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6-9, 21, 23, 24, 36, 37, 53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of predicting the likelihood of long-term survival of an ER positive breast cancer patient without the recurrence of breast cancer, comprising determining the expression of the RNA transcripts of MYBL2 or its expression products in an ER positive breast cancer cell obtained from said patient, normalized against the expression level of all RNA transcripts or their products in said ER positive breast cancer cell, or a reference set of RNA transcripts or their expression products, wherein increased expression of MYBL2 relative to a reference normal tissue indicates the decreased likelihood of long-term survival without breast cancer recurrence, does not reasonably provide enablement for such a method in any type of breast cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to

make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

The nature of the invention

The claimed invention is drawn to a method of predicting the likelihood of long-term survival of a breast cancer patient without the recurrence of breast cancer, comprising determining the expression level MYBL2, wherein the expression of MYBL2 indicates a decreased likelihood of long-term survival without breast cancer recurrence.

The breadth of the claim

The breadth of the claim is rather broad. The broadest claim encompasses a method of predicting longer-term survival of a patient with any type of breast cancer, and with or without any treatment by the mere presence of MYBL2 expression.

The teaching of the specification and the working examples provided

The specification teaches based on binary statistical analysis, MYBL2 is determined to have higher expression (Table 2) in invasive breast carcinoma which is ER positive. However, MYBL2 does not appear to have prognostic value in ER negative breast cancer based on the same statistical analysis which results are summarized in Table 3. The specification does not disclose whether the mere expression of said gene in the breast tissue in any type of breast cancer is indicative of a poor prognosis for said patient. Thus, the scope of the instant claim exceeds the teaching of the instant specification.

The state of prior art and the level of predictability in the art

The prior art teaches that there are many factors that need to be considered in order to develop a reliable genetic test. Shalon et al (US 2001/0051344 A1, Dec 13, 2001) teach that due

to variations in genetic make-up of unrelated individuals in a heterogeneous society, differences in the expression of a gene between any two individuals may or may not be significant (see page 10, paragraph [0155]). Shalon et al further teach that the larger the number of individuals tested, the more significant the remaining differences in gene expression become and samples from at least 5 and preferably 20-50 different test individuals are assayed to obtain statistically meaningful data showing a statistical elevation or reduction in report levels when compared to control levels (see page 10, paragraph [0156]). Shalon et al teach that the test average pattern is compared with a control average pattern on a microarray to identify test genes which show significantly, typically at least 2 fold and up to 100 fold or more, increase or decrease in gene expression level with respect to control levels for the same gene (see page 10, paragraph [0158]). Post filing art, Kroese et al (Genetics in Medicine, Vol. 6, pages. 475-480, 2004) teach genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined. Kroese et al teach that a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods. (e.g. page 476, 2nd column, last paragraph). Kroese et al teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (e.g. page 477, 1st column, 1st and 2nd full paragraph). Kroese et al teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to

complete a thorough evaluation of many genetic tests (e.g. page 479, 2nd column, last paragraph). Additional post filing art reveals that most gene association studies are typically wrong. Lucentini (The Scientist, Vol. 18, page 20, 2004) teach that it strikingly common for follow-up studies to find gene-disease associations wrong (e.g. page 2, 1st paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a complex disease there is only roughly a one-third chance that the study will reliably confirm the finding (e.g. page 2, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical method, should be included in the gene association studies (e.g. page 3, 2nd paragraph).

As indicated in a review article written by Murphy et al. (Pathology, 2005, Vol 37(4), pages 271-277), the use of gene expression profiling in breast cancer prognostication and prediction has not yet reached the stage where it can be implemented clinically (see page 275, 2nd col., 2nd paragraph). Murphy et al. assert "an array of confounding issues remains, including differences in patient selection, array technology and chemistry, and methods of analysis" and "validation of new markers must be performed in the context of perspective clinical trials in which the prognostic or predictive questions can be answered." Korfee et al. (Current Pharmacogenomics, 2005. Vol.3, pp.201-216) teach that breast cancer may be classified into different subtypes based on different gene expression including ER+ and ER- subtypes (see page 202, Table 1). Such classification indicates that prognosis for ER+ and ER- subtypes is different. Korfee et al. also indicate that although good or poor prognosis signature may be established in laboratory, the clinical outcome is unpredictable at present (see page 204, 1st col., 1st paragraph).

The experimentation required to practice the claimed method

In summary, use of gene profiling in breast cancer prognostication is still under active investigation wherein validation of the test is very important. Based on the teaching of prior art, the prognosis for a particular type of breast cancer is different from another subtype, ie. ER+ vs. ER-. Indeed, based on the disclosure of the instant specification, over-expression of MYBL2 is only implicated for decreased likelihood of recurrence of breast cancer in ER+ group, but not in ER- group. Based on the limited teaching of the instant specification, and the unpredictable nature of such genetic test, one of ordinary skill in the art would have to engage in undue experimentation to practice the method to its full scope. Therefore, the claimed invention is only enabled to the scope indicated above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21, 23, 36, 37, 53 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how to determine whether the likelihood of said long term survival has increased or decreased based on the statistical analysis. In other words, what type of the statistical result would indicate a good or poor prognosis for a breast cancer patient. Claim 23 is rejected because of its dependency on claim 21.

Regard claim 36, the recitation of "wherein the level of the...comprises the RNA transcript or the product of two or more housekeeping genes" renders the claim indefinite because it is unclear how a level can comprise genes. Claim 37 is rejected because of its dependency on claim 36.

Regarding claim 56, the recitation of "differential expression of MYBL2, wherein evidence of increased expression" renders the claim indefinite because it is unclear what is difference between the expression of MYBL2. In other words, in order to show an increased expression, or difference in expression, it must have some reference the sample may be compared to. The claim does not recite such a reference. Therefore, the claim is indefinite because one cannot determine whether a sample has increased or decreased expression.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X. Qian Ph.D. whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joe Woitach Ph.D. can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Celine X Qian Ph.D.
Examiner
Art Unit 1636

CELINE QIAN, PH.D.
PRIMARY EXAMINER